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Development of Uniform Protocol for Alopecia Areata Clinical Trials

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Developing a successful treatment for alopecia areata (AA), clearly has not been at the forefront of the agenda for new drug/device development among the pharmaceutical and medical device industry. The National Alopecia Areata Foundation (NAAF), a patient advocacy group, initiated a plan to facilitate and drive clinical research toward finding safe and efficacious treatments for AA. As such, Alopecia Areata Uniform Protocols for clinical trials to test new treatments for AA were developed. The design of the uniform protocol is to accomplish the development of a plug-and-play template as well as to provide a framework wherein data from studies utilizing the uniform protocol can be compared through consistency of inclusions/exclusions, safety, and outcome assessment measures. A core uniform protocol for use by pharmaceutical companies in testing proof of concept for investigational products to treat AA. The core protocol includes standardized title, informed consent, inclusion/exclusion criteria, disease outcome assessments, and safety assessments. The statistical methodology to assess successful outcomes will also be standardized. The protocol as well as the informed consent form has been approved in concept by Liberty IRB and is ready to present to pharmaceutical companies.

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INTRODUCTION

Developing a successful treatment for alopecia areata (AA) clearly has not been at the forefront of the agenda for new drug/device development among the pharmaceutical and medical device industry. Currently, no Federal Food and Drug Administration (FDA) approved therapy exists (Shapiro *et al.*, 1997; Lachgar *et al.*, 1998; Wiseman *et al.*, 2001; Olsen *et al.*, 2004; Blume-Peytavi *et al.*, 2011; Gilhar *et al.*, 2012). The National Alopecia Areata Foundation (NAAF), a patient advocacy group, initiated a plan to facilitate and drive clinical research toward finding safe and efficacious treatments for AA. NAAF, following FDA Guidelines (FDA, 2010), obtained support in principle from the FDA, to develop Alopecia Areata Uniform Protocols for clinical trials to test new treatments for AA. The design of the uniform protocol is meant to accomplish two overall goals: firstly, the uniform protocol is to be a plug-and-play template to entice biopharmaceutical and medical device companies to test medications and devices on AA. Secondly, the AAUP is to be a framework wherein data from clinical trials for the treatment of AA can be easily compared through consistency of inclusions/exclusions, safety, and outcome assessment measures.

RESULTS

A core protocol for a pharmaceutical investigative product proof of concept was developed and approved by the SAC.

The title accepted is ''Uniform Core Protocol for Phase (II /III) of A Double-Blind, Vehicle Controlled, Randomized, Multi-Center Study to Evaluate the Safety and Therapeutic Efficacy of <ENTER IP> Treatment of Adult Patients with Moderate to Severe Scalp Alopecia Areata.''

The calculation of power follows d1:d2: v (Treatment Dose 1: Treatment Dose 2: Vehicle) For a *P*-value percentage difference between treatment Dose 1 (d1), Dose 2 (d2), and vehicle (veh)-treated subjects on the primary efficacy end point, treatment d1, d2, and veh-treated subjects will be required to provide π% power with a two-sided test at a significance level of 0.05. Screened: d1 +d2 +v+σ Enrolled (Randomized): (d1 +d2 +v+σ) * % Planned Complete: d1 +d2 +v. (Dell *et al.*, 2002).

Primary objective is

The primary objective is to assess the safety and therapeutic efficacy of a 24-week regimen of administration of investigational products (IP) with x treatment frequency, in adult subjects with chronic moderate-to-severe scalp AA.

Secondary objectives include

Assessment of the durability of the response over a 12-week post-treatment period of observation; the subjects' perceptions of their scalp disease with treatment, and upon withdrawal of treatment, in relationship to baseline; the change from

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Abbreviations: AA, Alopecia areata; AT, Alopecia totalis; AU, Alopecia universalis; FDA, Federal Food and Drug Administration (USA); ICF, Informed Consent Form; IP, Investigative Product; NAAF, National Alopecia Areata Foundation; SAC, Scientific Advisory Committee; SALT, Severity of Alopecia Tool

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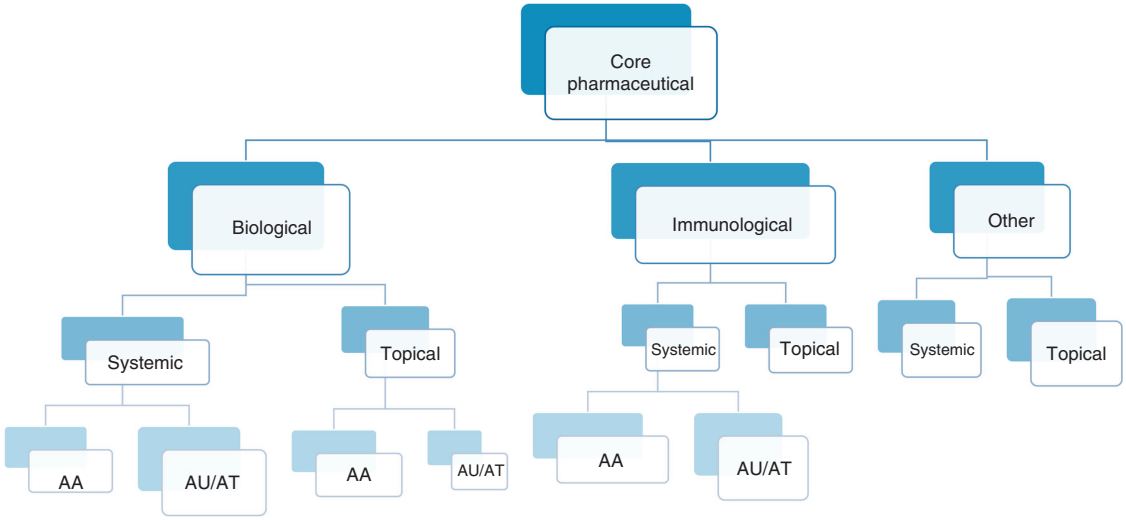


Figure 1. Map of core protocol for pharmaceutical investigative drug. The pharmaceutical company would edit this protocol with input specific to the investigative drug.

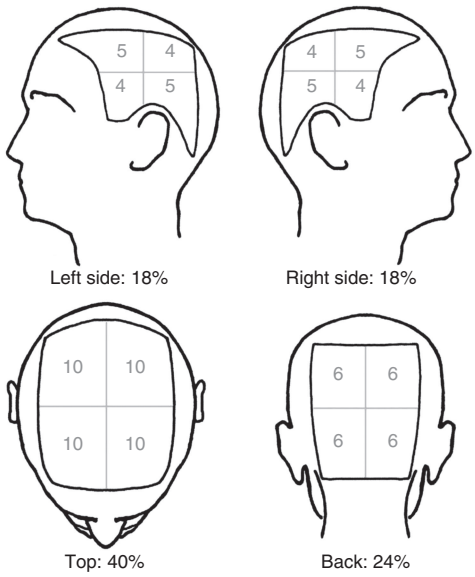
baseline of the number and width of terminal hairs in the target site using digital photography; and IP-specific changes in the biomarker associated with IP.

Inclusion criteria include
Subjects >18 years of age with a diagnosis of scalp AA and at least 25% scalp hair loss due to AA, for at least 6 months up to 2 years duration. All subjects taking thyroid medication or hormonal therapy must be on a stable dose for 6 months and maintain such throughout the study. Female subjects who are pregnant or who are nursing or plan pregnancy during the study period are restricted from participation.

Exclusion criteria include
Less than 25% scalp AA involvement; any co-existent androgenetic alopecia; prior treatment with IP; active scalp inflammation; history of systemic or cutaneous medical, or psychiatric disease which will put patient at risk or interfere with assessments.

Disease outcome assessments include
Severity of Alopecia Tool (SALT) score (Figure 1); digital photography; IP-related biomarkers, subject oriented AA assessments (Figure 2) Skindex, and Mendoza AA Qol Burden of Disease Questionnaire.

Safety assessments include
Adverse event history, changes in concomitant medications and/or diseases, physical exam, vital signs, electrocardiogram, chest X-ray, safety blood and urine labs, and IP-specific safety labs.



Olsen/Canfield

Salt score			
Site:	Subject:	Visit:	Date:
Quadrant	Percentage involved	Multiplier	Score
Left side		0.18	
Right side		0.18	
Top		0.40	
Back		0.24	
Total			

Figure 2. Severity of Alopecia Tool (SALT) score methodology (Reprinted from Olsen *et al.*, 2004 with permission from the *Journal of the American Academy of Dermatology*).

Analysis
The methods of analysis will be calculated according to standard statistical methods to maintain significance based on knowledge of the investigative product or device being tested. A minimal significance of $P<0.05$ two-tailed will be maintained. Wherein possible, one should justify the number of subjects with a preliminary power calculation, as published by Dell *et al.* (2002) for calculating sample size, using the formula $n=1+2C(s/d)2$, where $n=$number to enroll, C is

Alopecia areata is a condition that may affect you. Please rate how severe the following symptoms of your alopecia areata have been *in the past week*. Please select one response from 0 (symptom has not been present) to 10 (the symptom was as bad as you can imagine it could be) for each item.

	Not present										As bad as you can imagine
Scalp hair loss	0	1	2	3	4	5	6	7	8	9	10
Body or eye lashes hair loss	0	1	2	3	4	5	6	7	8	9	10
Tingling/numbness of the scalp	0	1	2	3	4	5	6	7	8	9	10
Itchy or painful skin	0	1	2	3	4	5	6	7	8	9	10
Irritated skin	0	1	2	3	4	5	6	7	8	9	10
Feeling anxious or worry	0	1	2	3	4	5	6	7	8	9	10
Feeling sad	0	1	2	3	4	5	6	7	8	9	10

Your alopecia areata may interfere with your daily functioning. Please rate how the following items were interfered with by alopecia areata *in the past week*. Please select one response from 0 (did not interfere) to 10 (interfered completely) for each item.

	Did not interfere										Interfered completely
Work	0	1	2	3	4	5	6	7	8	9	10
Enjoyment of life	0	1	2	3	4	5	6	7	8	9	10
Interaction with others	0	1	2	3	4	5	6	7	8	9	10
Daily activities	0	1	2	3	4	5	6	7	8	9	10
Sexual relationships	0	1	2	3	4	5	6	7	8	9	10
Quality of life	0	1	2	3	4	5	6	7	8	9	10

Figure 3. **Alopecia Areata Symptom Impact Scale (AASIS).**

constant dependent on desired power and significance, *s* is SD, and *d* is difference to detect.

In summary, the development of the AA core uniform protocols and their modules hopefully will encourage and facilitate the testing of new drugs and devices in patients with AA. Moreover, the uniformity of the process will allow for comparisons between and among treatments studied. Thus, by having uniform protocols available for industry, more treatments can be developed and tested with an improved ability to compare the efficacy of one treatment or another for each and all of the AA variants.

MATERIALS AND METHODS

Members of the NAAF Scientific Advisory Committee (SAC) provided historical protocols for a variety of previous AA investigations. The SAC concurred with an overall plan to develop a uniform protocol made up of two core uniform protocols for all forms of A one for pharmaceutical agents, and another for medical devices. Since there are no currently FDA approved treatments for AA, the initial core protocols are developed for proof of concept investigations. The core has a standardized title, power of study, informed consent form (ICF), inclusion/exclusion criteria set, outcome assessments, and safety assessments.(Olsen *et al.*, 2004; Blume-Peytavi *et al.*, 2011; Olsen, 2011; Gilhar *et al.*, 2012) In light of variable responses that may occur between those patients with patchy AA from those with alopecia totalis (AT) and/or alopecia universalis (AU), subjects with AT (>95% scalp) or AU (>95% scalp as well as diffuse non-scalp involvement) are included, but are evaluated as separate groups from those with patchy (25–95%) alopecia.

From these core protocols, modules can be developed for specific variants in mode of application (topical, oral, injected) frequency of application (twice daily, monthly), pharmacological /immunological concepts; device modus of administration (laser, non-laser). A pharmaceutical or device company may then modify these modules with factors specific to the investigative product or device (Figure 3).

Corresponding to this core protocol also developed were an ICF, and source documents. The protocol and ICF were presented to Liberty IRB, Deland FL and approved in concept.

CONFLICT OF INTEREST

Grant from NAAF (patient advocacy group) went to the author's employer to develop Uniform Protocol. The authors declare no conflict of interest.

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DISCLAIMER

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